Docket No.: EISN-009US
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Rulin Fan

Application No.: 10/546,132 | Confirmation No.: 9915

Filed: December 12, 2005 | Art Unit: 1623

For: REAGENTS AND METHODS FOR PREPARING LPS ANTAGONIST B1287 AND STEREOISOMERS THEREOF | Examiner: R. P. Issac

DECLARATION UNDER 37 CFR §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, James E. Foy, Ph.D., declare:

1. I am not an inventor of the above-identified application. However, I make this declaration to further prosecution of the application. Rulin Fan, the inventor of the above-identified application, worked under my supervision at Eisai Research Institute of Boston, Inc. (hereinafter "Eisai Research Institute") from January 2000 until July 2007, during which period this method was developed.

2. I received a B.S. degree in Chemistry from the University of Colorado in 1972, and a Ph.D. in Chemistry from Pennsylvania State University in 1976. Additionally, I spent two years conducting post-doctoral research in organic chemistry at Cornell University.

3. I have extensive research experience in the area of synthetic organic chemistry, with an emphasis in process development, as demonstrated by my curriculum vitae (attached as Exhibit A). I worked as a Senior Scientist in Plastics Research and in Biocides Research and Process Development at Rohm and Haas Company from 1978 to 1980 and 1980 to 1986, respectively. In 1986, I became an Associate Senior Investigator in Chemical Development at SmithKline

Beecham, where I was promoted to Project Manager in 1988 and again promoted to Assistant Director in 1990, where I remained until 1996. I also worked as a consultant for SmithKline Beecham in Chemical Development from 1996 to 1997. From 1997 to 2000 I was a Senior Research Associate in the Fine Chemicals Group of PPG Industries. I have been a Senior Scientist in Eisai Research Institute's Process Research department since 2000. Eisai Research Institute is a wholly-owned subsidiary of Eisai Corporation of North America, which is a wholly-owned subsidiary of Eisai Co., Ltd., the current assignee of the present application. In my current capacity I work in Process Research.

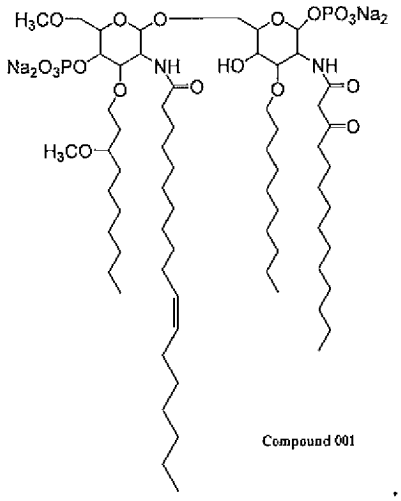
4. I have carefully read and understand the contents of the above-identified patent application. I have also carefully read and understand two Office Actions from the U.S. Patent and Trademark Office, the first mailed February 20, 2007 and the second mailed November 2, 2007, as well as U.S. 6,184,366 which was cited as prior art in these Office Actions. The Office Actions state that the pending claims (*i.e.*, claims 120-123, 125-128, 130-133 and 135-138) of the above-identified patent application are "rejected under 35 U.S.C. 103(a) as being unpatentable over" the cited reference. I have reviewed the pending claims, attached hereto as Exhibit B. For the reasons provided below, I believe that the invention defined by the claims set forth in Exhibit B, is neither taught nor suggested by the reference cited in the Office Action, or by the general knowledge known to one of ordinary skill in the art, at the time the application was filed.

5. The Office Actions cite U.S. 6,184,366 as teaching "the synthesis of liposaccharides with strong structural similarity to compounds of the present invention." (Office Action mailed February 20, 2007, page 4 and Office Action mailed November 2, 2007, page 2) Specifically, U.S. 6,184,366 is cited as teaching compounds differing from the compounds of the present invention by the addition or removal of substituents from the saccharide structures. The cited reference is based, at least in part, on a process that was developed at Eisai Research Institute.

6. The present invention is based upon an improvement of that the process disclosed in U.S. 6,184,366, which improvement was also developed at Eisai Research Institute. It was unexpected at the time the claimed invention was made that this improvement would lead to a feasible process. For example, when this improvement was suggested to the Process Research department by the inventor of the above-identified application, the general belief within the

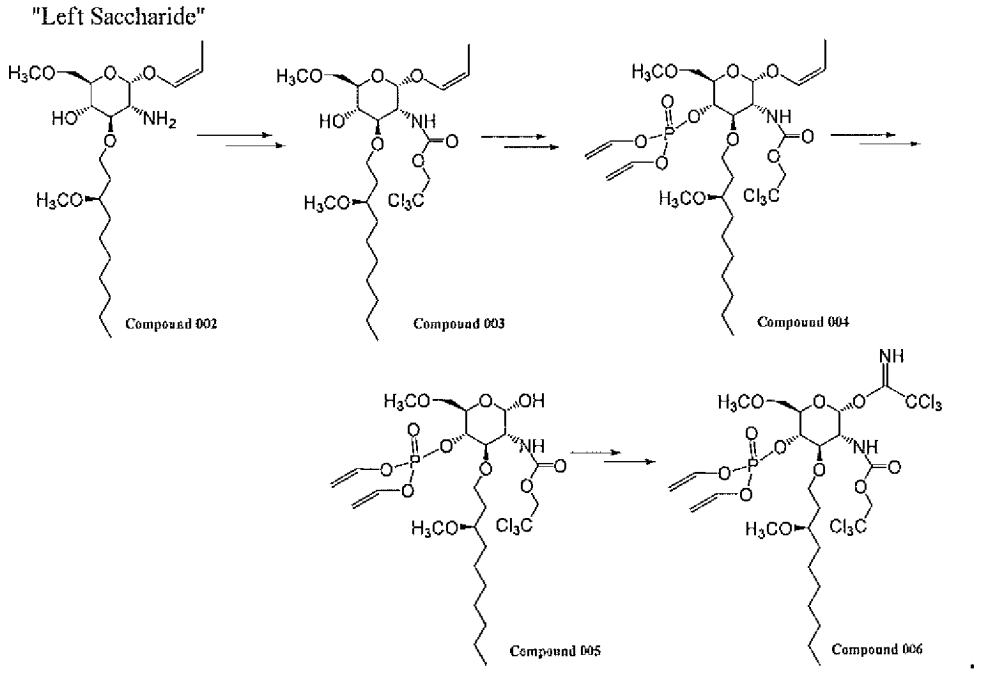
department was that such an improved process would not be possible, as discussed in more detail below.

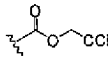
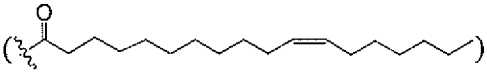
7. It is my understanding that the invention set forth in pending claims 120-123, 125-126, 128, 130-133, 135-136 and 138 of this patent application relates to compounds which can be used, for example, as intermediates corresponding to the "left saccharide" portion and the "right saccharide" portion of compounds of the following formula:



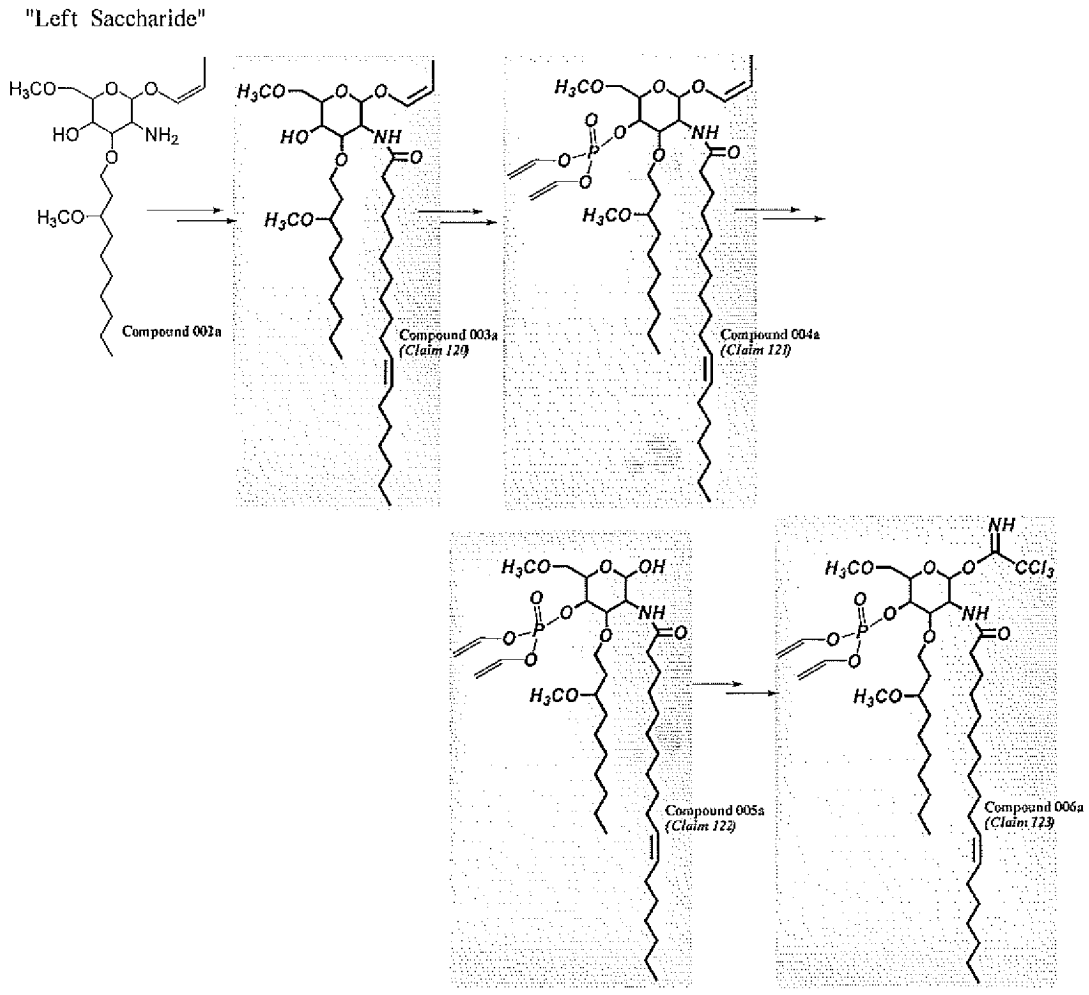
Compound 001

8. With regard to the "left saccharide", it is my understanding that U.S. 6,184,366 provides, in pertinent part, the following general synthetic method:



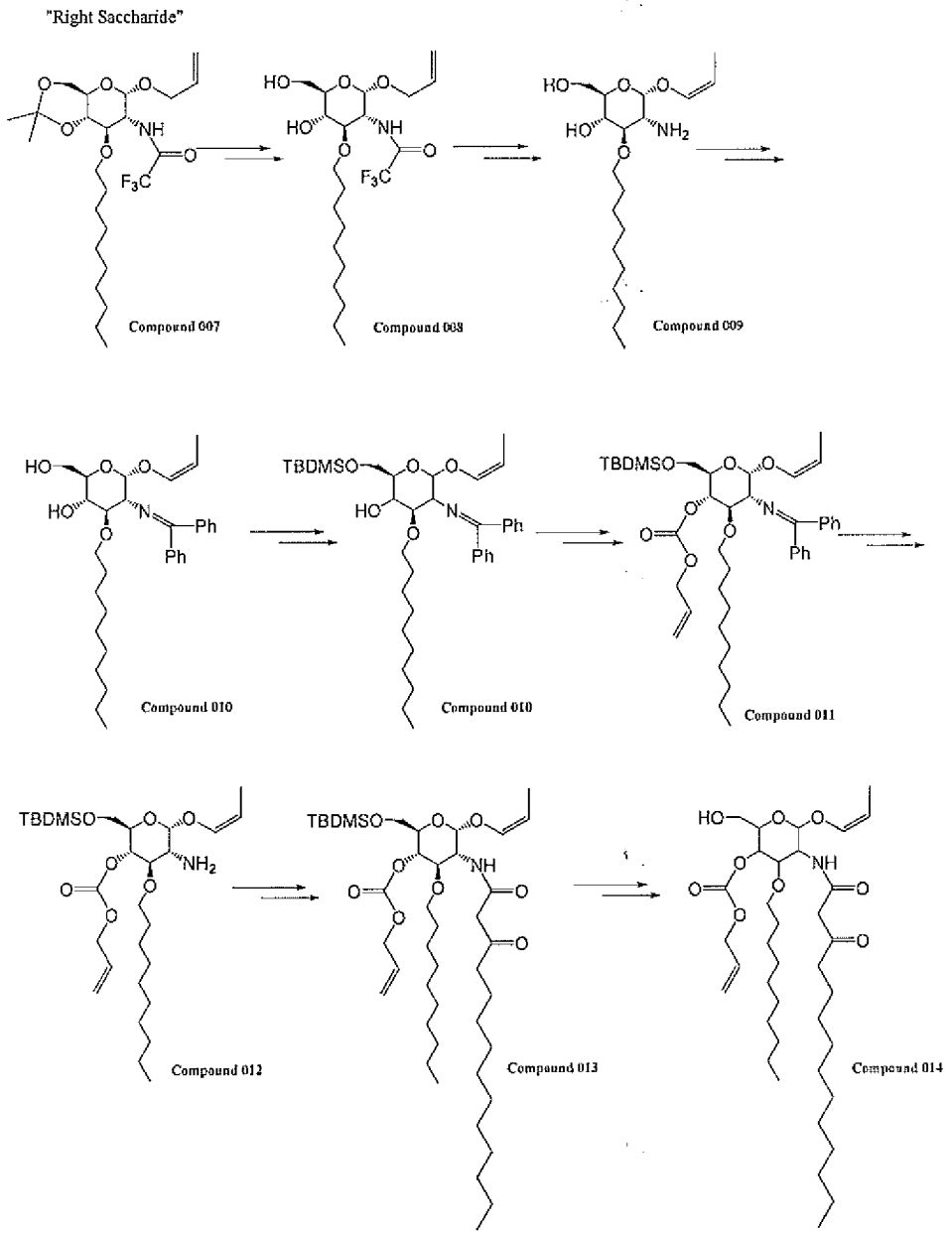
In this process, the amino substituent is protected by a Troc moiety (*i.e.*, ) and a left alkanoyl group () is not added until after the introduction of a phosphate group and after the coupling of the right saccharide to the left saccharide. See, *e.g.*, U.S. 6,184,366, columns 34 through 36 and 46.

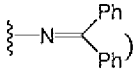
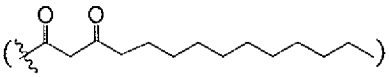
9. The present invention provides new and unobvious intermediates which are prepared using new and unobvious methods for synthesizing the left saccharide where the left alkanoyl group is added early in the synthesis, prior to the introduction of the phosphate group and prior to the coupling with the right saccharide. The new intermediates, highlighted in grey below, are used in the following new methods, shown in pertinent part:



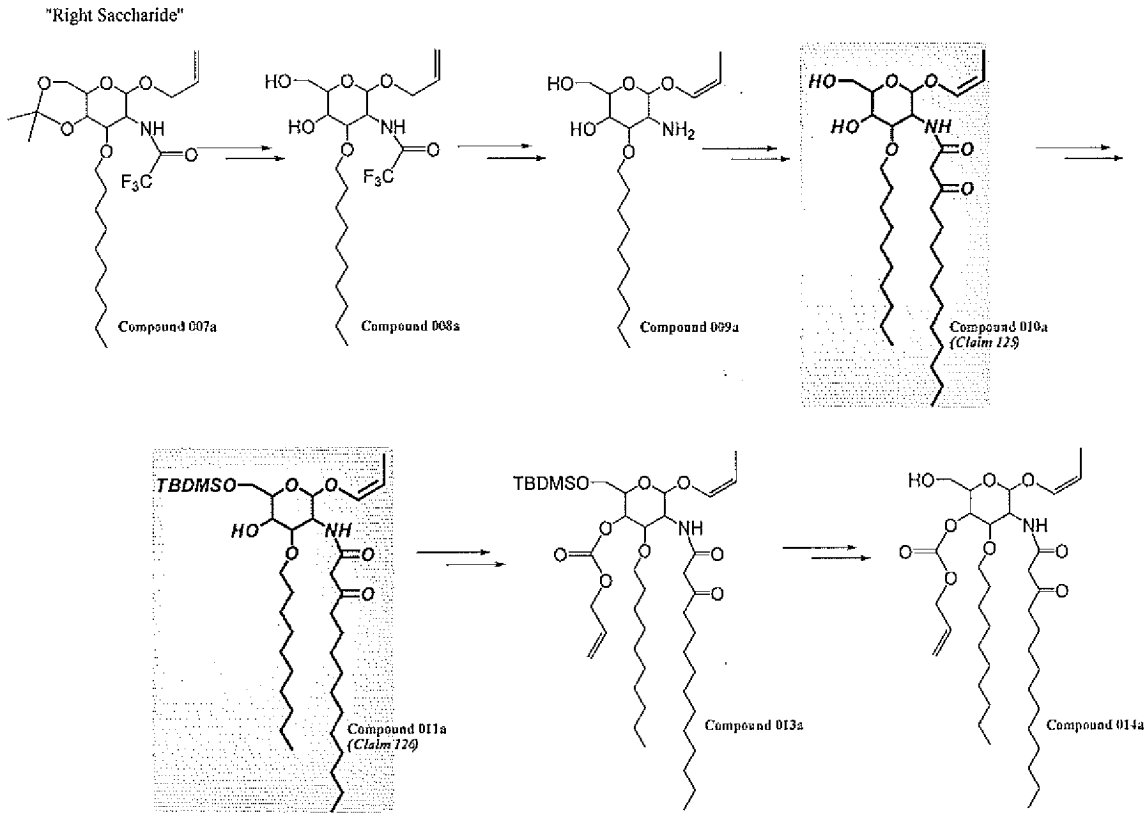
The new methods and intermediates described immediately above make it possible to synthesize the left saccharide portion of the Compound 001, shown in 7 above, and couple it to the right saccharide portion of the same compound in significantly fewer steps than the methods of U.S. 6,184,360. The new intermediates and methods avoid protection and deprotection steps disclosed in that patent, such as the addition and removal of the Troc moiety described in 8, above. By using fewer steps, the new methods reduced the number and quantity of reagents needed and increased the overall yield.

10. With regard to the "right saccharide", it is my understanding that U.S. 6,184,366 provides, in pertinent part, the following general synthetic method:

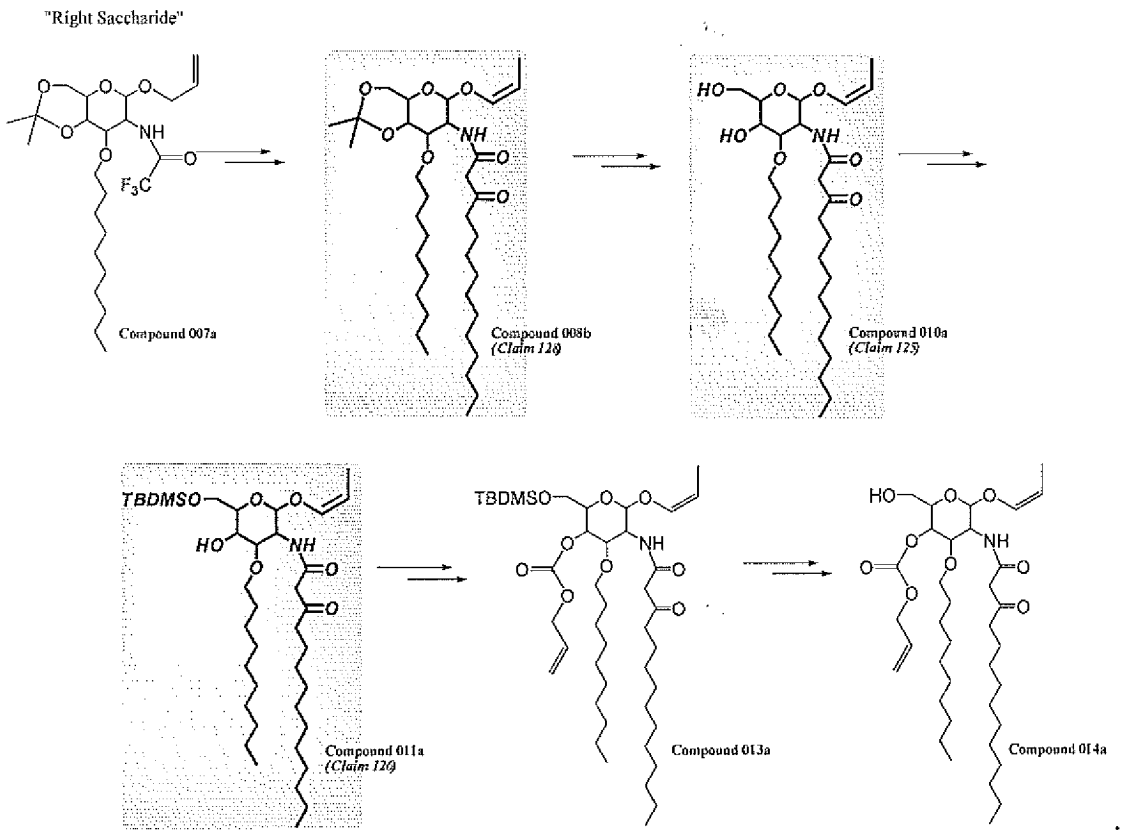


In this process, the amino substituent is protected by a diphenylimine moiety (*i.e.*, ) and a right alkanoyl group () is not added until after the introduction of an allyl ester group. See, *e.g.*, U.S. 6,184,366, columns 37 through 45.

11. The present invention provides new and unobvious intermediates which are prepared using new and unobvious methods for synthesizing the right saccharide where the right alkanoyl group is added early in the synthesis, prior to the introduction of the allyl carbonate group. The new intermediates, highlighted in grey below, are used in either of the following new methods, shown in pertinent part:



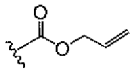
or:



The new methods and intermediates described immediately above make it possible to synthesize the right saccharide portion of the Compound 001, shown in 7 above, in significantly fewer steps than the methods of U.S. 6,184,360. The new intermediates and methods avoid protection and deprotection steps disclosed in that patent, such as the addition and removal of a diphenylimine moiety described in 10, above. By using fewer steps, the new methods reduced the number and quantity of reagents needed and increased the overall yield.

12. All intermediates highlighted above are shown as general formulae, as in claims 120-123, 125, 126, and 128 of Exhibit B. A stereospecific form of each highlighted intermediate is shown in claims 130-133, and 135, 136 and 138 of Exhibit B. As indicated above, I believe that none of the intermediates listed in Exhibit B were taught or suggested by U.S. 6,184,366, alone or in combination with general knowledge in the art, at the time the application was filed. As of the filing date of the present application, a person of ordinary skill in the art would have found it unexpected that that the alkanoyl groups could act as protecting groups, and that the compounds protected with alkanoyl groups would be suitable as intermediates in the processes described

herein. This belief was based, at least in part, on the potential reactivity of the alkanoyl-protected intermediates with reagents utilized in the synthesis of the disaccharide compound shown in paragraph 7 (*e.g.*, phosgene, Oxone® (Du Pont), etc.), as discussed in more detail herein. Thus, there was no motivation prior to the present invention to modify the left or right intermediates with the left or right alkanoyl groups prior to the introduction of such potentially reactive reagents, *e.g.*, during the addition of an allyl ester group moiety or a phosphate group.

13. Phosgene is utilized in the addition of the allyl ester moiety (*i.e.*, ) in the synthesis of the right saccharide. This is true of both the present method and the methods disclosed in U.S. 6,184,366. Phosgene, Cl_2CO, is extremely reactive with amine nitrogens (*e.g.*, readily forming isocyanates). In order to prevent the reaction of phosgene with the primary amine groups, a protecting group on the nitrogen of the right saccharide was believed to be necessary. As illustrated in U.S. 6,184,366, diphenylimine is suitable for use as a protecting group in a phosgene addition step. Phosgene, however, may also react with an amide bond to form an imidochloride, as disclosed in U.S. Patent No. 3,282,923 (attached hereto as Appendix C). In the present method, the addition of the right alkanoyl group to the right saccharide would form an amide bond. Prior to the present invention, one of ordinary skill in the art could not have predicted that phosgene would not attack the amide bond formed upon coupling of the right alkanoyl group and the right saccharide. Accordingly, there would have been no reason for a person of ordinary skill in the art to modify the right saccharide compounds of U.S. 6,184,366 in the particular manner described in the present methods.

14. Oxone® is utilized in the addition of the phosphate moiety in the synthesis of the left saccharide. This is true of both the present method and the methods disclosed in U.S. 6,184,366. Oxone® can oxidize amine nitrogens to nitrosoalkanes and/or oximes. In order to prevent the reaction of Oxone® with the primary amine groups, a protecting group on the nitrogen of the left saccharide was believed to be necessary. As illustrated in U.S. 6,184,366, Troc is suitable for use as protecting groups in an Oxone® addition step. Oxone®, however, may also react with an alkene to form an epoxide, as disclosed in Bloch, R. *et al.*, *J Org. Chem.* 50:1544-45 (1985) (attached hereto as Appendix D). In the present method, the left alkanoyl group possesses an alkene in the chain. Prior to the present invention, one of ordinary skill in the art could not have predicted that Oxone® would not attack the alkene introduced into the intermediate upon

coupling of the left alkanoyl group and the left saccharide. Accordingly, there would have been no reason for a person of ordinary skill in the art to modify the left saccharide compounds of U.S. 6,184,366 in the particular manner described in the present methods.

15. In sum, as of the filing date of the present invention, a person of ordinary skill in the art would have found it unexpected that the long chain alkanoyl groups would act as a protecting group in the presence of reagents utilized in the synthesis of the disaccharide compound shown in paragraph 7, such that the alkanoyl-protected intermediate could survive the remainder of the synthesis to the final product. Thus, as of the filing date of the present invention, a person of ordinary skill in the art would have found it unexpected that the synthesis of the disaccharide could successfully proceed through the route described in the present invention (*e.g.*, the route without a Troc or diphenylimine intermediate). Accordingly, the fact that the compounds listed in Exhibit B could be successfully synthesized would also have been unexpected to a person of ordinary skill in the art in view of the art that was available at the time of the filing of the application, including U.S. 6,184,366.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made may be punishable by fine or imprisonment, or both, and that such willful false statements may jeopardize the validity of this Application for Patent or any patent issuing thereon.

Dated: June 13, 2006 Signature: DRAFT James E Fall

Exhibit A

James E. Foy, PH. D.

1 Alpine Drive ~ Andover, MA 01810
Work Phone: 978-837-4718 ~ Home Phone: 978-470-3902 ~ Email: james_foy@erl.eisai.com

SUMMARY

PH. D. organic chemist with 20 years of experience in Research and Development and Manufacturing departments of pharmaceutical and chemical companies. Extensive hands-on experience with all aspects of new synthetic route discovery, process development, scale-up to pilot plants, technology transfers and implementation of full scale manufacturing processes for bulk pharmaceuticals and fine chemicals. Proven ability to work with cross functional teams. Bottom line oriented problem solver with a solid record of technical and managerial contributions.

Served as project champion of international multi-discipline project teams implementing changes to existing manufacturing processes as well as new processes. Led several projects to develop processes to make pharmaceutical intermediates and Active Product Ingredient (APIs)

WORK HISTORY

Eisai Research Institute, Andover, MA (2000 to present)
Senior Scientist, Process Research

PPG INDUSTRIES, INC., Monroeville, PA (1997 – 2000)
Senior Research Associate, Fine Chemicals Group

Project leader for process development of an API and intermediates for the pharmaceutical industry. Assisted sales and marketing with technical presentations to customers. Managed technology transfers to manufacturing sites. Supervised six scientists

SMITHKLINE BEECHAM, King of Prussia, PA (1986 -1997)

Consultant, Chemical Development (August 1996 to February 1997)

Defined new process for an antimalarial that reduced the number of steps from seventeen to twelve.

Assistant Director, Chemical Development (1990 - August 1996)

Project Champion for seven projects on discovery and implementation of manufacturing processes for drug substances and intermediates. Supervised six scientists.

Project Manager, Chemical Development (1988 - 1990)

Responsible for development and implementation of changes in manufacturing process for cimetidine, the active ingredient in SmithKline Beecham's major antiulcer product, Tagamet, which improved quality, lowered cost and increased productivity. Supervised three scientists.

Associate Senior Investigator, Chemical Development (1986 - 1988)

Managed and planned the chemistry of a project which resulted in improved quality, and lower cost of the bulk pharmaceutical.

Exhibit A

James E. Foy, PH. D.

ROHM AND HAAS COMPANY, Spring House, PA (1978-1986)

Senior Scientist, Biocides Research and Process Development (1980 - 1986)

Discovered and synthesized novel organic compounds for broad spectrum biocide activity. Developed two new processes and successfully scaled them up to pilot and intermediate scale.

Senior Scientist, Plastics Research Department (1978 - 1980)

Responsible for discovery and development of abrasion resistant coatings.

EDUCATION

Cornell University, Ithaca, New York (I 976 - 1978) Advisor: Professor Bruce Ganem

Post Doctorate/Complete Fifteen Step Synthesis of "Southwestern Zone" of Maytansine

Pennsylvania State University, State College, Pennsylvania (1972 - 1976) Advisor: Professor Maurice Shamma

Ph.D., Organic Chemistry/isolation, Identification and Synthesis of New Alkaloids

University of Colorado, Boulder, Colorado (1 968 - 1972)

B.A., Chemistry/Completed One Year of Advanced Research with Professor Tad Koch

CONTINUING EDUCATION

Current Good Manufacturing Practices (cGMPs)
Several courses on communication and management skills
Statistics for experimenters
Statistical Quality Control
Courses in crystallization and heterocyclic chemistry

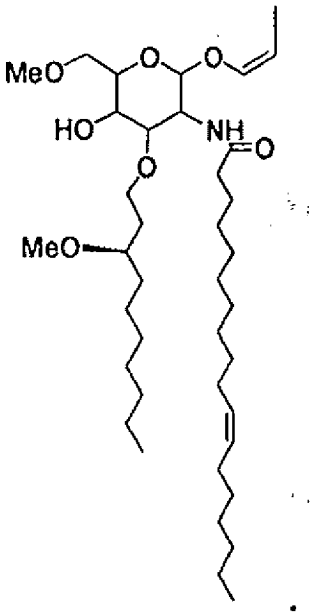
ORGANIZATIONS

American Chemical Society
North Shore Amateur Astronomy Club (President and Star Party Coordinator)
Boy Scouts of America: Leadership positions for eleven years

Exhibit B

CLAIMS AS CURRENTLY PRESENTED

120. (Original) A compound having the structure:



121. (Original) A compound having the structure:

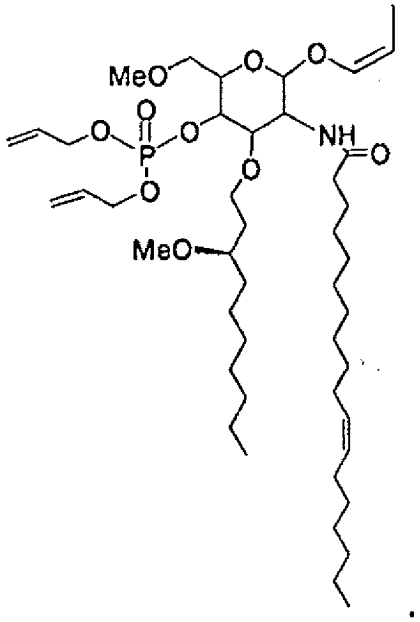
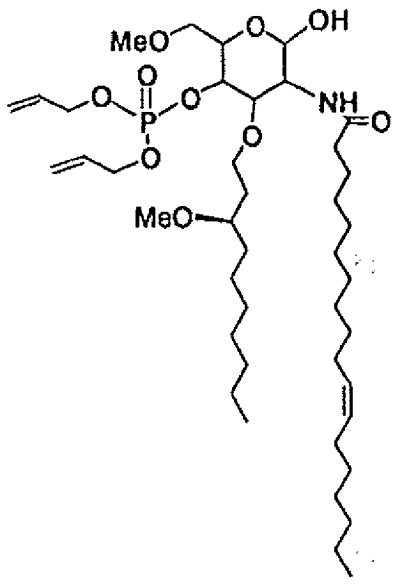


Exhibit B

122. (Original) A compound having the structure:



123. (Original) A compound having the structure:

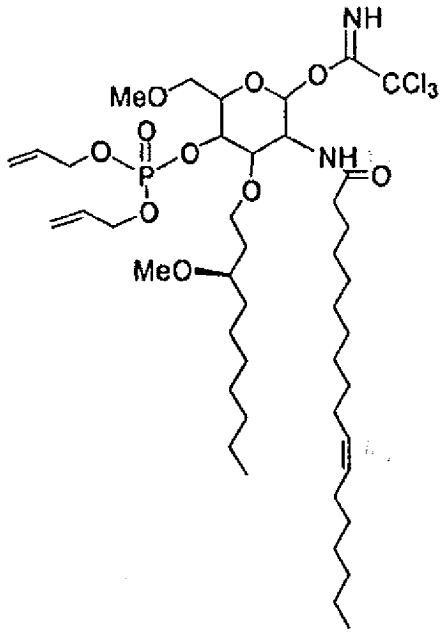
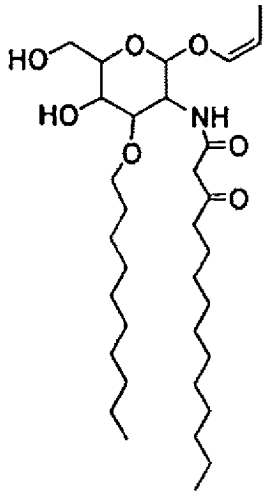


Exhibit B

125. (Original) A compound having the structure:



126. (Original) A compound having the structure:

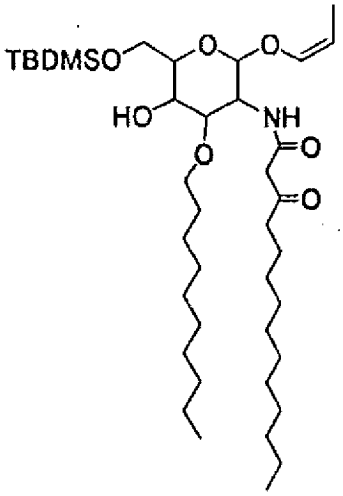
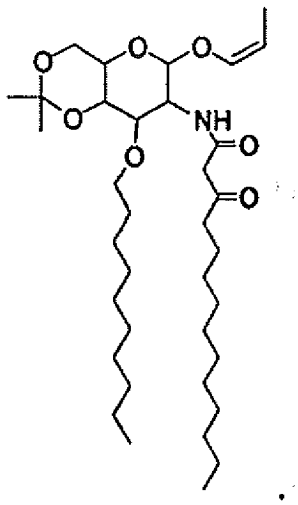


Exhibit B

128. (Original) A compound having the structure:



130. (Original) The compound of claim 120 having the structure:

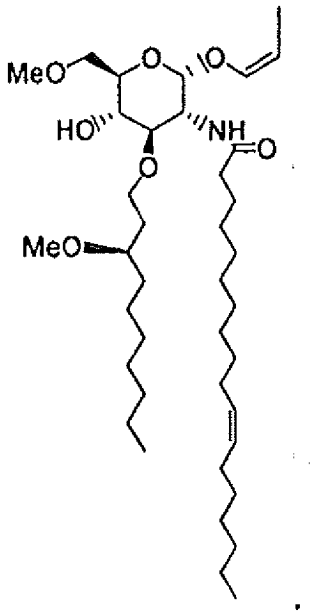
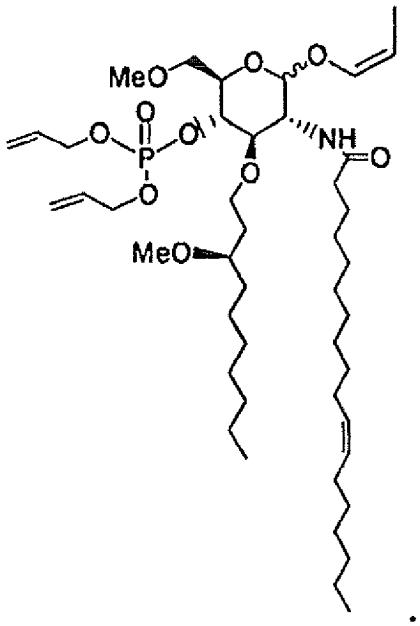


Exhibit B

131. (Original) The compound of claim 121 having the structure:



132. (Original) The compound of claim 122 having the structure:

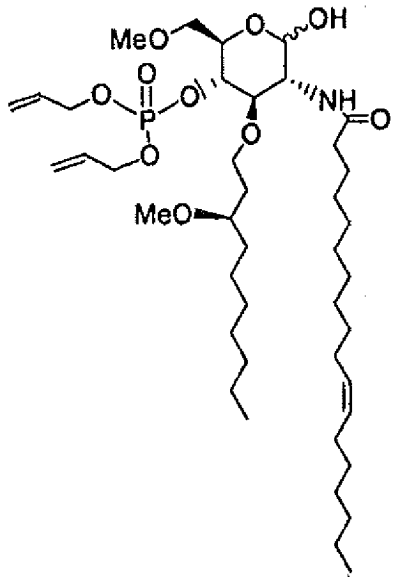
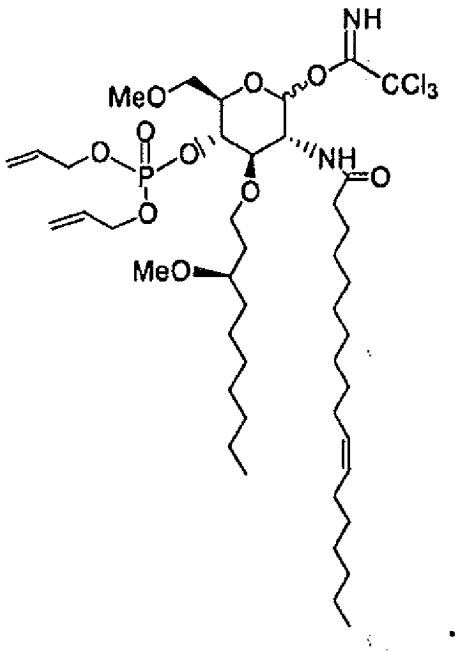
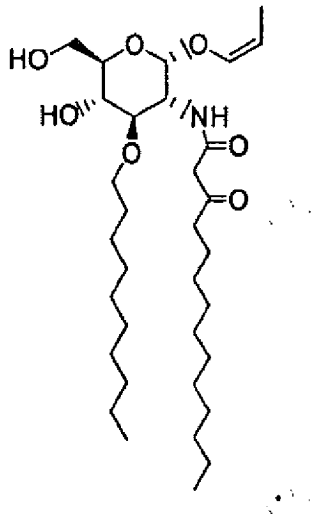


Exhibit B

133. (Original) The compound of claim 123 having the structure:

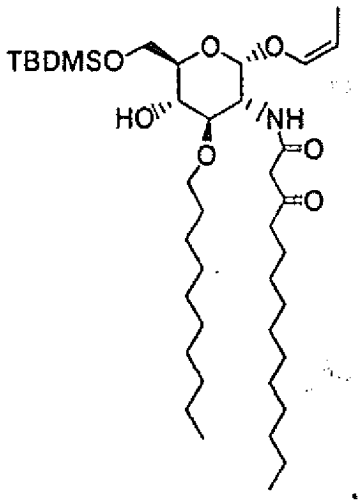


135. (Original) The compound of claim 125 having the structure:



136. (Original) The compound of claim 126 having the structure:

Exhibit B



138. (Original) The compound of claim 128 having the structure:

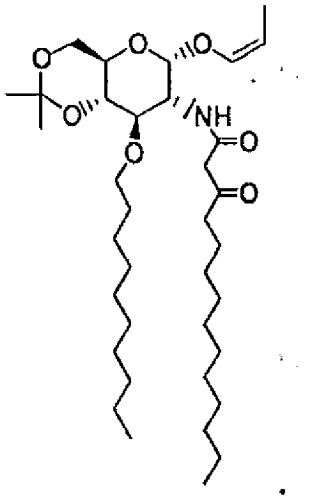


Exhibit C

United States Patent Office 3,282,923 Patented Nov. 1, 1966

3,282,923

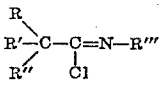
PROCESS FOR THE PREPARATION OF IMIDOCHLORIDES AND/OR HYDROCHLORIDES OF IMIDOCHLORIDES

Johannes H. Ottenheym, Sittard, and Johan W. Garritsen, Geleen, Netherlands, assignors to Stamicarbon N.V., Heerlen, Netherlands

No Drawing. Filed Oct. 30, 1961, Ser. No. 148,730
Claims priority, application Netherlands, Oct. 31, 1960, 257,446, 257,447
11 Claims. (Cl. 260—239)

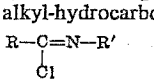
The invention relates to a process for the preparation of imidochlorides and/or hydrochlorides of imidochlorides with the exception of imidochloride compounds in which both the carbon atom and the nitrogen atom of the carbonimide groups is directly bound to an aryl or alkaryl group. The invention relates particularly to compounds satisfying one of the following general formulae and to hydrochlorides thereof:

(a)



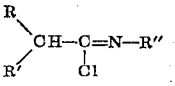
where R, R', R'' and R''' represent identical or non-identical lower alkyl, hydrocarbon aryl, hydrocarbon aryl lower alkyl and lower alkyl-hydrocarbon aryl;

(b)



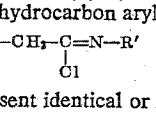
where R represents a cyclic lower alkyl, hydrocarbon aryl and lower alkyl-hydrocarbon aryl and R' lower alkyl and hydrocarbon aryl lower alkyl;

(c)



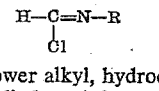
where R, R' and R'' represent identical or non-identical lower alkyl, hydrocarbon aryl, hydrocarbon aryl lower alkyl and lower alkyl-hydrocarbon aryl;

(d)



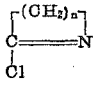
where R and R' represent identical or non-identical lower alkyl, hydrocarbon aryl, hydrocarbon aryl lower alkyl and lower alkyl-hydrocarbon aryl, and where R may also represent a hydrogen atom;

(e)



where R represents lower alkyl, hydrocarbon aryl, hydrocarbon aryl lower alkyl and lower alkyl-hydrocarbon aryl;

(f)



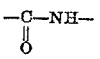
where n has a value >2.

It is known that some of these imidochlorides can be prepared by reaction of corresponding N-mono-substituted acid amides with compounds containing phosphorus and chlorine, e.g. PCl_5, PCl_3, $POCl_3$ or mixtures of these compounds. This method of preparation has the drawback that by-products, in the form of compounds containing phosphorus, are formed which have to be removed from the reaction mixture and this involves an extra treatment in the purification of the desired final product. In addition, it has usually proved impossible, especially with the imidochlorides satisfying the abovementioned general Formulae *d*, *e*, and *f*, to isolate the imidochlorides and/or their hydrochlorides from the resulting reaction mixtures, since these substances are very liable to decompose.

Furthermore it has been proposed, especially for the preparation of the imidochlorides included under the abovementioned general Formulae *b*, *d*, *e* and *f*, to introduce phosgene into a solution of the corresponding N-mono-substituted acid amides. However, the yield of imidochlorides obtained by this process is low (e.g. the yield of 2-chloro-1,2-azacyclohepten from ε-caprolactam is 28%). In addition, neither with this process has it been proved that the corresponding imidochlorides and/or their hydrochlorides have actually been formed, as either the reaction products of the phosgenation reaction were immediately converted into more stable products or products were isolated that could not be conclusively identified as imidochlorides and/or their hydrochlorides.

It has now been found that imidochlorides, having the moiety

and/or hydrochlorides of imidochlorides, with the exception of the imidochlorides in which both the carbon and the nitrogen atom of the carbonimide group is directly bound to an aryl or alkaryl group, can be prepared in a simple way and with a high yield by reacting the corresponding N-mono-substituted acid amides having the moiety



with phosgene in the presence of a solvent in such a way that at all times or at substantially all times during the course of the reaction at least one mole of phosgene is present per mole of acid amide, with the proviso that in the event that the acid amide is one in which at least one hydrogen atom is bound to the carbon atom adjacent to the carbon amide group or in which the carbon amide group is bound only to hydrogen atom, the said molar ratio does not exceed 2:1.

In general, by-products formed in this reaction are CO_2, which readily escapes from the reaction mixture, and HCl, which can escape or form a hydrochloride with the imidochloride formed. When a hydrochloride is formed, this can be separated off and used as such.

The process according to the invention is carried out in such a way that throughout the reaction at least one mole of phosgene is present per mole of acid amide, which in the case of those acid amides in which no hydrocarbon atom is bound to the carbon atom adjacent to the carbon amide group means either that the acid amide can be added gradually to a solution of the appropriate total amount of phosgene, or that both the reaction components can be fed simultaneously to the reaction zone in at least equimolar amounts.

With the other acid amides on the other hand the process has to be carried out in such a way that throughout the reaction at most two moles of phosgene are present per mole of acid amide, since reaction of these acid amides with larger amounts of phosgene yields N-substituted carbamyl chlorides. The latter reaction has already been described in the Belgian patent specification 582,478 filed in the name of the applicant for the preparation of 2 - chloro - azacyclo-2,3-alkene-1-carbochlorides starting from ω-lactams. In the case of the abovementioned acid amides therefore the process can be realized only by feeding the two components simultaneously to a reaction zone in such a ratio that at least one and at most two moles of phosgene will be present per mole of acid amide.

The preparation of imidochlorides from N-substituted acid amides tends to present the most difficulty with the imidochlorides covered by the aforesaid general Formulae *a* and *b* and those compounds of general Formula *c* in which R'' represents an aryl or alkaryl group.

It is therefore recommended in the preparation of these groups of imidochlorides to maintain at all times during the reaction a molar ratio of phosgene to the acid amide of at least 1.8:1. In the preparation of the other imidochlorides e.g. those of general Formulae *d*, *e* and *f* and the other compounds of Formula *c*, on the other hand the amount of phosgene present throughout the reaction should preferably be smaller, viz. 1–1.3 moles per mole of acid amide.

It is not necessary before the reaction to free the phosgene used from any small amounts of hydrogen chlorides which it may contain and it is even preferable not to do so, since it appears that the hydrogen chloride has a catalytic effect on the reaction.

The process according to the invention is carried out in the presence of a solvent for the phosgene, which solvent is inert to the reactants and reaction products under the reaction conditions and which is preferably also capable of dissolving the acid amide. Suitable solvents are, e.g. hydrocarbons, such as benzene and toluene, and in particular halogenated hydrocarbons, such as chloroform, carbon tetrachloride, chlorobenzene and dichlorobenzene.

It is recommended that the reaction be carried out at atmospheric pressure, so that it is possible to use simple apparatus. However, it may also be advantageous to use a slightly elevated pressure during the reaction, e.g. ¼, ½ or 1 at. gauge.

In the preparation of imidochlorides and hydrochlorides thereof covered by the aforesaid general Formulae *a* and *b* and those compounds of general Formula *c* in which R'' represents an aryl or alkaryl group, the reaction temperature may be chosen from within wide limits; it may be kept for instance between 0 and 100° C., although higher temperatures may also be used. Below 0° C. the reaction rate will become too low in most cases. As a rule it is recommendable during the first part of the reaction, when the reaction components are brought into contact with each other, to keep the temperature at a lower level, say at 20–40° C., and subsequently to raise it to, say, 40–100° C. for a secondary reaction period in which the highest possible degree of conversion is reached.

In the preparation of the other imidochlorides and hydrochlorides thereof, however, the reaction temperature is preferably kept below 40° C. to avoid side-reactions, but generally preferably not below 0° C. A preferable way of carrying out the process for preparing these imidochlorides and hydrochlorides thereof involves the reacting components, that is to say the acid amide, or a solution thereof, and a solution of phosgene being simultaneously and continuously introduced into a reaction zone in which the temperature is 20–40° C. and from which the reaction product is continuously discharged and immediately cooled to a temperature below 20° C.

In view of the high sensitivity of the imidochlorides, or the hydrchlorides thereof, to moisture it is recommended to exclude moisture as completely as possible during the whole preparation, and also to keep the products obtained without moisture.

The imidochlorides and/or hydrochlorides can be prepared according to the invention in a simpler way and, generally, with a higher yield than is possible by using the prior proposed techniques. The present invention makes it possible to isolate, either as such and/or in the form of their hydrochlorides, a number of imidochlorides the existence of which has up to now only been postulated but not yet proved, or which have not yet been postulated.

The imidochlorides and/or hydrochlorides of imidochlorides prepared according to the invention are valuable intermediate products, from which, by further conversions, important substances can be obtained. For instance, reaction with primary and secondary amines, yields amidines which are used in the preparation of dyestuffs and pharmaceuticals. By reaction with chlorine

gas or another chlorinating agent and hydrolysis of the product formed thereby the imidochlorides satisfying the general Formula *d* or *f* aforesaid can be converted into α,α-dichloro-amides, or α,α-dichlorolactams, from which, by further reactions, amino-acids important for nutrition or high molecular weight products with plastic properties can be prepared.

The resulting imidochlorides and/or hydrochlorides may, if so desired, be purified by recrystallization or distillation, and, provided moisture is completely excluded, be kept in this condition for a considerable period of time, but in most cases such a purification can be omitted since the substances prepared by the process according to the invention can be converted to final useful products without any further treatment being required. With regard to the imidochlorides satisfying the abovementioned general Formula *c* when R'' therein represents an alkyl or aralkyl group, or *d*, *e* or *f*, it is even recommendable to subject these imidochlorides to further conversions without further purification where possible to restrict losses owing to intermediate decomposition. An excess of phosgene, if used, as well as the solvent employed can be recovered during processing of the reaction product and may be re-used.

It appears that acid amides of aromatic or alkylaromatic carboxylic acids, in which the nitrogen atom is also bound to an aryl or alkaryl group do not react with phosgene under the conditions of the process according to the invention. Accordingly, we make no claim to reactions in which acid amides of this category are used.

The invention will be further explained with reference to the following examples, which, however, are not meant to limit its scope in any way whatsoever.

Example 1

400 ml. of benzene are measured into a spherical 1 liter reaction vessel provided with a stirrer and a reflux cooler through which ice-water is pumped during the experiment, and 150 g. of phosgene are dissolved therein. A solution of 78.5 g. of N-butyl-pivalamide (N-butyl-trimethylacetamide) in 150 ml. of benzene is added to this solution in one hour, the temperature in the reaction vessel being kept at 30–40° C. Subsequently, the temperature of the reaction mixture is raised to 40–60° C. and kept at this level for 4 hours during which period a portion of the excess of phosgene distils over.

Upon completion of the reaction the remaining phosgene and the benzene are removed by distillation under normal pressure. The residue is fractionated at a pressure of 12 mm. Hg. At 65° C. the N-butyl-pivalimidochloride distils over as a colourless liquid with a refractive index $n_D^{20}=1.4440$ (54.5 g.). After that, an amount of 26.3 g. of unconverted N-butyl-pivalamide distils over at 120–122° C. The efficiency calculated to converted acid amide therefore amounts to 93.4%. The substance is identified by elementary analysis and infrared spectrometry.

Example 2

250 ml. of chloroform are measured into the reaction vessel used in Example 1 and 250 g. of phosgene are dissolved therein. In a period of 1 hour a solution of 163 g. N-propyl-benzamide in 250 ml. of chloroform are added to the above solution, the temperature in the reaction vessel being kept at 25–30° C. Subsequently, the temperature of the reaction mixture is gradually raised to 60° C. in 1.5 hr. and kept at this level for 4 hours. Upon completion of the reaction the remaining phosgene and the chloroform are removed by distillation under normal pressure and the residue is distilled off at a pressure of 2 mm. Hg. The resulting N-propyl-benzimidochloride distils over at 84° C. as a colourless liquid with a refractive index of $n_D^{20}=1.5421$. The yield amounts to 179 g., which corresponds to an efficiency of 98.6%. The substance is identified by elementary analysis and infrared spectrometry.

Example 3

In the same way as described in Example 2 a solution of 135 g. N-methyl-benzamide in 150 ml. of chloroform is added to a solution of 200 g. of phosgene in 400 ml. of chloroform at room temperature in a period of 1 hour. Subsequently, the temperature is gradually raised to 60° C. and kept at this level for another 5 hours. Upon removal of the remaining phosgene and chloroform by distillation at normal pressure the residue is distilled at a pressure of 1 mm. Hg. At 67° C. the N-methyl benzimidochloride distils over as a colourless liquid with a refractive index of $n_D^{20}=1.5625$. The yield is 149 g., i.e. the efficiency amounts to 97.1%. The substance is identified by elementary analysis and infrared spectrometry.

Example 4

A solution of 100 g. of phosgene in 200 ml. of chloroform and a solution of 81.5 g. of N-phenyl-isobutyramide in 200 ml. of chloroform are introduced simultaneously into the reaction vessel mentioned in Example 1 in a period of 1 hour, the temperature in the reaction vessel being kept at 25–30° C. Subsequently, the temperature of the reaction mixture is gradually raised to 60° C. in 2½ hours and kept at this level for 3 hours.

After completion of the reaction the remaining phosgene and the chloroform are removed by distillation at normal pressure and the residue is distilled at a pressure of 3 mm. Hg. At 76° C. the resulting N-phenyl-isobutyrimidochloride distils over as a colourless liquid with a refractive index of $n_D^{20}=1.5380$ at 76° C. The yield amounts to 70.5 g., which corresponds to an efficiency of 77.7%. The substance is identified by means of elementary analysis and infrared spectrometry.

Example 5

In the same way as described in Example 4 a solution of 100 g. of phosgene in 250 g. of chloroform and a suspension of 101.5 g. of N-phenylhexahydrobenzamide in 250 ml. of chloroform are introduced into the reaction vessel in one hour, the temperature in the reaction vessel being kept at 35° C. Subsequently, the temperature is gradually raised to 55–60° C. in two hours, and kept at this level for 3 hours.

After the excess of phosgene and the chloroform have been distilled off at normal pressure, the residue is distilled at a pressure of 1 mm. Hg. At 122–123° C. the resulting N-phenyl-hexahydrobenzimidochloride distils over as a colourless liquid ($n_D^{20}=1.5528$). The yield is 90 g., which is equivalent to an efficiency of 81.3%. The substance is identified by elementary analysis and infrared spectrometry.

Example 6

Into the same reaction vessel as used in the previous examples, a solution of 55 g. of phosgene in 300 ml. of dry ether and a solution of 64.5 g. of N-butyl-propionamide are introduced in a period of 1 hour at a temperature of about 20° C. Subsequently, the reaction is allowed to continue for 5 hours, after which the remaining phosgene and the ether are expelled from the reaction vessel by means of dry nitrogen, and the last traces are removed by means of a high-vacuum pump.

There remains 73.5 g. of light-yellow liquid (i.e., the theoretical yield) which is identified as N-butyl-propionimido-chloride by means of a chlorine determination and infrared spectrometry.

Example 7

Into the same reaction vessel as used in the previous examples, a solution of 55 g. of phosgene in 300 ml. of carbon tetrachloride and a solution of 57.5 g. of N-propyl-propionamide in 150 ml. of carbon tetrachloride are introduced in a period of 1 hour at a temperature of about 20° C., after which the reaction is allowed to continue for 5 hours at room temperature. The remaining phosgene and the carbon tetrachloride are subsequently expelled by means of dry nitrogen and the last traces are removed by means of a high-vacuum pump.

The weight of the light-yellow liquid left amounts to 68.5 g., which is slightly more than the theoretical yield. This is due to a small amount of carbon tetrachloride, which is not completely removed in high vacuo either. Identification by means of infrared spectrometry shows that the substance is N-propyl-propionimidochloride.

Example 8

In the same way as described in the previous examples, solutions of 100 g. of phosgene in 250 ml. of chloroform and 67.5 g. of acetanilide in 250 ml. of chloroform are introduced into the reaction vessel in one hour at a temperature of about 20° C. After half an hour already a solid crystalline substance forms in the reaction mixture with evolution of heat. After the reaction has been allowed to continue for 3 hours at 25–30° C., this solid substance is filtered off and dried under dry nitrogen. The weight of this substance is 51.5 g. and the melting point 119–121° C. If this substance is mixed with the hydrochloride of acetanilide, no depression is observed in the determination of the melting point and the identity of the two substances also appears from infrared spectrometry. The amount of isolated salt corresponds to 60% of the starting product.

Upon evaporation in vacuo at 20–30° C. the mother liquor of the filtered product yields a residue of 30 g. of a light-yellow liquid which is very hygroscopic and unstable. By means of infrared spectrometry this substance is identified as almost pure N-phenyl-acetimidochloride. The yield calculated to acetanilide is consequently about 39%.

Example 9

A solution of 59 g. of N-methyl formamide in 200 ml. of benzene and a solution of 200 g. of phosgene in 300 ml. of benzene are introduced in a period of 1 hour into the same reaction vessel as used in the preceding examples. The reaction mixture is subsequently raised to a temperautre of about 40° C. and kept at this temperature for 5 hours.

After completion of the reaction the remaining phosgene is expelled by means of dry nitrogen and the resulting precipitate is filtered off and dried under nitrogen. 70 g. of white crystalline product with a melting point of 160–162° C. is obtained which, by means of a chlorine determination and infrared spectrometry, is identified as the hydrochloride of N-methyl formimidochloride. Consequently the yield calculated to N-methyl formamide is 61.4%.

Example 10

A solution of 56 g. of phosgene in 400 ml. of carbon tetrachloride and a solution of 56.5 g. of ε-caprolactam in 150 ml. of carbon tetrachloride are introduced in one hour at a temperature of about 20° C. into the same reaction vessel as used in the preceding examples, after which the reaction is allowed to continue for 6 hours at this temperature.

After completion of the reaction the precipitate formed is filtered off and dried in an atmosphere of dry nitrogen. 76 g. of white crystalline product with a melting point of 66–70° C. (determined in a closed tube) is obtained. By means of chlorine determination and infrared spectrometry the substance is identified as the hydrochloride of 2-chloro-1,2-azacycloheptene (caprolactimidochloride). Consequently, the yield is 90.5%, while an amount of the salt remains dissolved in the mother liquor.

Example 11

A cylindrical reaction vessel of 50 ml. capacity is provided with a stirrer, a reflux cooler through which ice-water is pumped during the experiment, two feed openings in the top and one discharge opening in the bottom. 25

ml. of chloroform is fed into this vessel and subsequently a solution of 57.5 g. of N-propyl-propionamide in 150 ml. of chloroform and a solution of 50 g. of phosgene in 150 ml. of chloroform are simultaneously added in one hour, the reaction mixture being continously drained from the bottom of the vessel so that the vessel always remains half-full. The temperature in the reaction vessel is kept at 20–25° C. and the reaction mixture is discharged into a collector which is kept at about 18° C. and is provided with a vent hole on which a tube with a drying agent is placed.

Upon completion of the reaction the resulting N-propyl-propionimidochloride is converted into the corresponding amidine by introducing the whole contents of the collector in one hour into a stirred solution of 140 g. of aniline in 250 ml. of chloroform. The temperature is then kept at about 30° C. and after addition of the imidochloride, the reaction is allowed to continue for about half an hour at about 40° C. The reaction mixture is then separated into two layers, the aqueous layer is made alkaline with sodium hydroxide solution and subsequently extracted with benzene. From the resulting benzene solution the solvent is distilled off at normal pressure and the residue is distilled at a pressure of 1 mm. Hg. Following the first runnings of aniline the N-propyl-N'-phenyl-propionamidine distils over at 122° C. as a colourless oil (n_D^{20}=1.5510). The yield amounts to 77 g., which corresponds to an efficiency of 81.0% calculated to the N-propyl-propionamide. The yield of imidochloride is consequently at least 81%. The amidine is characterized by means of elementary analysis and infrared spectrometry.

Example 12

In the same reaction vessel and in the same way as described in Example 11 as solution of 56.5 g. of ε-caprolactam in 150 ml. of chloroform is reacted for one hour with a solution of 50 g. of phosgene in 150 ml. of chloroform at a temperature of 20–25° C. The reaction mixture is drained off into a collector which is kept at about 18° C.

After completion of the reaction the resulting 2-chloro-1,2-azacycloheptene is converted into the corresponding amidine by allowing the whole contents of the collector, in the same way as described in Example 11, to react with 140 g. of aniline in 250 ml. of chloroform and processing the reaction mixture in the same way. At a pressure of 1–2 mm. Hg and at 126–128° C., the 2-anilido-1,2-azacycloheptene distils over as a colourless oil which solidifies to yield a substance with a melting point of 102° C. Recrystallization from cyclohexane gives a white crystalline substance with a melting point of 105° C., which is further characterized by means of elementary analysis. The yield amounts to 81 g., which corresponds to an efficiency of 86.2% calculated to ε-caprolactam. The yield of imidochloride is consequently at least 86.2%.

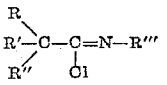
Example 13

In the same way as described in Example 12 a solution of 2 chloro-1,2-azacycloheptene in chloroform is prepared from 113 g. of ε-caprolactam in 250 ml. of chloroform and 100 g. of phosgene in 250 ml. of chloroform. Chlorine gas is subsequently passed into this solution at a rate allowing it to be completely absorbed. The temperature of the solution is kept below 30° C. When chlorine is no longer absorbed (after about half an hour), the reaction mixture is kept at 25° C. for one more hour after which the chloroform is distilled off at reduced pressure and at a temperature below 40° C. The liquid residue is poured onto ice and after 1 hour's stirring the water is decanted and the remaining crystal mass is filtered off, washed with cold ether, and dried. 128 g. of α,α-dichlorocaprolactam with a melting point of 122–123° C. are obtained. The efficiency calculated to ε-caprolactam is 70.3%.

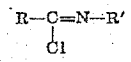
In a similar experiment the chlorination is carried out by adding the solution of the imidochloride in 2 hours to 1 litre of sulphuryl chloride at 25–30° C., then gradually raising the temperature of the reaction mixture to 60° C. in 2 hours, and keeping the reaction mixture at this temperature for one more hour. After distilling off at reduced pressure the chloroform and the excess of sulphuryl chloride, pouring onto ice, decanting, filtering off, washing, and drying, 160 g. of α,α-dichloro-caprolactam with a melting point of 121–122° C. are obtained. Efficiency: 88.0%.

We claim:

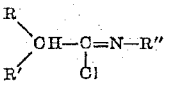
1. A process for the preparation of a member of the group consisting of imidochlorides having one of the following formulae:

(a) 

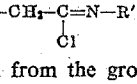
wherein R, R', R'' and R''' are substituents selected from the group consisting of lower alkyl, hydrocarbon aryl, hydrocarbon aryl lower alkyl and lower alkyl-hydrocarbon aryl;

(b) 

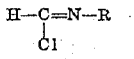
wherein R is selected from the group consisting of cyclic lower alkyl, hydrocarbon aryl and lower alkyl-hydrocarbon aryl and R' is selected from the group consisting of lower alkyl and hydrocarbon aryl-lower alkyl;

(c) 

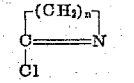
wherein R, R' and R'' are selected from the group consisting of lower alkyl, hydrocarbon aryl, hydrocarbon aryl lower alkyl and lower alkyl-hydrocarbon aryl;

(d) 

wherein R is selected from the group consisting of hydrogen, lower alkyl, hydrocarbon aryl, hydrocarbon aryl lower alkyl and lower alkyl-hydrocarbon aryl, and R' is selected from the group consisting of lower alkyl, hydrocarbon aryl, hydrocarbon aryl lower alkyl and lower alkyl-hydrocarbon aryl;

(e) 

wherein R is selected from the group consisting of lower alkyl, hydrocarbon aryl, hydrocarbon aryl lower alkyl and lower alkyl-hydrocarbon aryl; and

(f) 

wherein *n* has a value >2, and the hydrochlorides of said imidochlorides, said process comprising the steps of reacting the corresponding N-monosubstituted acid amide with phosgene in the presence of an inert organic solvent and maintaining throughout said reaction at least one mole of phosgene per mole of acid amide with the proviso that the molar ratio of phosgene to acid amide is between 1:1 and 2:1 when preparing the compounds represented by Formulae *c–f*, and then recovering the respective imidochloride.

2. Process according to claim 1 wherein the acid amide is one which is free of hydrogen bound to the carbon atom adjacent to the carbonamide group and at least 1.8 moles of phosgene are present throughout the reaction.

3. Process according to claim 1 wherein the acid amide is one which has one hydrogen atom bound to the carbon atom adjacent to the carbonamide group and 1.8–2.0 moles of phosgene are present per mole of acid amide.

4. Process according to claim 1 wherein the acid amide corresponds with one of the compounds defined by Formulae *d*, *e* and *f* and from 1.0 to 1.3 moles of phosgene are present throughout the reaction per mole of acid amide.

5. Process for the preparation of 2-chloro-1,2-azacycloheptene which comprises gradually adding ε-caprolactam to a solution of phosgene in an organic solvent selected from the group consisting of chloroform, carbon tetrachloride, benzene, chlorobenzene, dichlorobenzene and toluene, the molar ratio of phosgene to ε-caprolactam being kept within the range of 1.0:1 to 1.3:1, at substantially all times during the course of the reaction.

6. Process according to claim 1, characterized in that the solvent used is capable of dissolving both the phosgene and the acid amide under the reaction conditions.

7. Process according to claim 1, characterized in that the reaction is carried out at atmospheric pressure.

8. Process according to claim 1, characterized in that during the reaction of the acid amide the temperature of the reaction mixture is kept at a value between 0 and 100° C.

9. Process according to claim 8, characterized in that during the first part of the reaction period the temperature of the reaction mixture is kept between 20 and 40° C. and during the remainder of the said period between 40 and 100° C.

10. Process according to claim 4, characterized in that during the reaction of the acid amide the temperature of the reaction mixture is kept at a value between 0 and 40° C.

11. Process according to claim 10, characterized in that the reaction components are simultaneously and continuously introduced into a reaction zone, in which the temperature is kept between 20 and 40° C. and from which the reaction product is continuously discharged and immediately cooled to a temperature below 20° C.

References Cited by the Examiner

UNITED STATES PATENTS

2,836,592 5/1958 Anagnostopoulos et al. ... 260—239

OTHER REFERENCES

Australian Abstract: 52,807/59, Mar. 17, 1960.

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Ethyl 3-carbethoxythiochromone-2-acetate (5b) was prepared from **1a** (1 mmol) and **2b** (168 mg, 1 mmol) by method C and was purified by recrystallization.

Anal. Calcd for $C_{16}H_{16}O_5S$: C, 59.98; H, 5.03. Found: C, 59.79; H, 4.94.

Ethyl 3-carbethoxychromone-2-acetate (5c) was prepared from **1a** (1 mmol) and **2c** (152 mg, 1 mmol) by method C. Column chromatography gave pure **5c**; exact mass calcd for $C_{16}H_{16}O_6$ 304.0945, found 304.0939.

Ethyl 3-carbethoxy-4-phenylquinoline-2-acetate (5d) was prepared from **1a** (3 mmol) and **2d** (591 mg, 3 mmol) by method A. Column chromatography gave pure **5d**, identical in all respects with an authentic sample.

Ethyl 3-carbethoxy-4-methylquinoline-2-acetate (5e) was prepared from **1a** (3 mmol) and **2e** (405 mg, 3 mmol) by method A. Column chromatography gave pure **5e**; exact mass calcd for $C_{17}G_{19}NO_4$ 301.1314, found 301.1329. The picrate salt was prepared for combustion analysis.

Anal. Calcd for $C_{23}H_{22}N_4O_{11}$: C, 52.08; H, 4.18; N, 10.56. Found: C, 52.19; H, 4.12; N, 10.43.

Ethyl 3-carbethoxyquinoline-2-acetate (5f) was prepared from **1a** (1 mmol) and **2f** (121 mg, 1 mmol) by method A. Recrystallization gave pure **5f**, identical in all respects with an authentic sample.[6]

Ethyl 3-carbethoxy-4-hydroxythiophene-2-acetate (5g) was prepared from **1a** (2 mmol) and **2g** (212 mg, 2 mmol) by method B. Column chromatography gave pure **5g**.

Anal. Calcd for $C_{11}H_{14}SO_5$: C, 51.15; H, 5.46; S, 12.42. Found: C, 51.04; H, 5.52; S, 12.51.

Ethyl 3-carbethoxy-4-hydroxy-5-methylthiophene-2-acetate (5h) was prepared from **1a** (4 mmol) and **2h** (448 mg, 4 mmol) by method B. Column chromatography gave pure **5h**.

Anal. Calcd for $C_{12}H_{16}O_5S$: C, 52.93; H, 5.92; S, 11.77. Found: C, 53.02; H, 6.08; S, 11.99.

Ethyl 4-carbethoxy-1,5-diphenylpyrazole-3-acetate (5i) was prepared from **1a** (1 mmol) and **2i** (212 mg, 1 mmol) by method A. Column chromatography gave pure **5i**, identical in all respects with an authentic sample.[7]

Ethyl 4-carbethoxy-5,6-diphenylpyridazine-2-acetate (5j) was prepared from **1a** (1.5 mmol) and **2j** (336 mg, 1.5 mmol) by method A. Column chromatography gave pure **5j**; exact mass calcd for $C_{23}H_{22}N_2O_4$ 390.1577, found 390.1571.

Registry No. **1a**, 52358-42-6; **2a**, 85-91-6; **2b**, 4892-02-8; **2c**, 119-36-8; **2d**, 2835-77-0; **2e**, 551-93-9; **2f**, 529-23-7; **2g**, 2365-48-2; **2h**, 53907-46-3; **2i**, 579-45-3; **2j**, 5344-88-7; **5a**, 73286-07-4; **5b**, 95421-53-7; **5c**, 95421-54-8; **5d**, 17282-92-7; **5e**, 23301-16-8; **5f**, 95421-55-9; **5g**, 95421-56-0; **5h**, 95421-57-1; **5i**, 41470-68-2; **5j**, 95421-58-2.

Supplementary Material Available: IR and NMR spectra of compounds in Table I (1 page). Ordering information is given on any current masthead page.

Epoxidation of Alkenes with Potassium Hydrogen Persulfate

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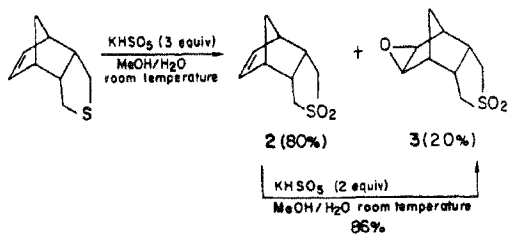
Potassium hydrogen persulfate ($KHSO_5$, potassium caroate), commercially sold as oxone, is a convenient, inexpensive, and powerful oxidant with a wide range of application.[1] It has been recently reported that alkenes[2,3] as well as arenes[4] can be epoxidized by dioxirane intermediates generated in situ by the reaction of potassium hydrogen persulfate with acetone. In the absence of ketones no reaction was observed under the reaction conditions used by the authors. We report now that potassium hydrogen persulfate alone is able to epoxidize water-soluble or insoluble alkenes with good to excellent yields, thus opening a new, efficient, and simple way for epoxide synthesis.

This work was initiated by the fact that in contrast with Trost's report[5] we observed the partial epoxidation of an isolated double bond by $KHSO_5$ in aqueous methanol: up to 20% of epoxide **3** was formed during the reaction of 4-thiatricyclo[5.2.1.$0^{2,6}$]dec-8-ene (**1**) with oxone at room temperature.[6]



When the sulfone **2** was treated with 2 equiv of oxone in the same conditions, a 86% yield of epoxide **3** was obtained after 24 h. These observations led us to examine the epoxidation of various alkenes with potassium hydrogen persulfate in aqueous methanol. The results are summarized in Table I.

In procedure A the reaction medium is acidic (pH 2–3) and only a few epoxides are stable under these conditions (entries 3 and 9). In the other cases this procedure led to products arising from oxirane ring-opening, and epoxidations were best performed by using method B or C where the pH is adjusted to 6 and kept at this value during the whole reaction by controlled addition of an aqueous solution of potassium hydroxide. This pH value was preferred to the one (pH 7.5) used for epoxidation with the caroate/acetone system[2] since the peroxide autodecomposition is much less at pH 6: for example, the yield of 1,2-epoxycycloheptane (**5**) was only 60% when the oxidation was made at pH 7.5 with 2 equiv of $KHSO_5$.

Cyclododecene (entry 4) failed to react with $KHSO_5$ in aqueous methanol, and this result may be due to the lack of solubility of this alkene in the medium. The solubility criterion might account for the differences between the Trost[5] and Curci[2] reports and this work.

No methanol was necessary for the oxidation of a water-soluble olefin like sorbic acid (entry 8). In this particular case the formation of 4,5-epoxy-2-hexenoic acid (**11**) as the unique reaction product is representative of the high selectivity of the oxidation which is confirmed by the lack of reactivity of *trans*-cinnamic acid.

However, the reaction of 4-vinylcyclohexene (entry 5) is not so clean, and we could not avoid the formation of 20% diepoxide even when only 1 equiv of persulfate was used.

Experimental Section

Equipment and Materials. ^1H NMR spectra were measured on Perkin-Elmer R-12A or Perkin-Elmer R-32 spectrometers. IR spectra were run on a Perkin-Elmer 682 instrument. Mass spectra were obtained on a Hewlett-Packard 5992A GC/MS spectrometer. Controlled pH experiments were performed by using a Metrohm

(1) Kennedy, R. J.; Stock, A. M. *J. Org. Chem.* **1960**, *25*, 1901.
(2) Curci, R.; Fiorentino, M.; Troisi, L.; Edwards, J. O.; Pater, R. H. *J. Org. Chem.* **1980**, *45*, 4758 and references cited therein.
(3) Cicala, G.; Curci, R.; Fiorentino, M.; Laricchiuta, O. *J. Org. Chem.* **1982**, *47*, 2670.
(4) Jeyaraman, R.; Murray, R. W. *J. Am. Chem. Soc.* **1984**, *106*, 2462.
(5) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287.
(6) Bloch, R.; Abecassis, J. *Tetrahedron Lett.* **1982**, *23*, 3277.

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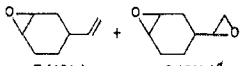
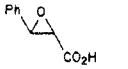
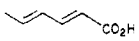
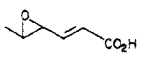
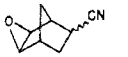
Table I. Reaction of Alkenes with Potassium Hydrogen Persulfate

entry	alkene	method[a]	reactn time, h	$KHSO_5$,[b] equiv	product		yield,[c] %
1	cyclohexene	B	5	2	1,2-epoxycyclohexane (4)		62
2	cycloheptene	B	4	2	1,2-epoxycycloheptane (5)		91
3	cyclooctene	A	4	1.5	1,2-epoxycyclooctane (6)		94
4	cyclodecene *E* + *Z*	A or B	5	2	no reaction		
5		B	5	1	 7 (46%) 8 (21%)[d]		
		B	5	2	7 (40%) 8 (60%)[d]		
		B	5	5	8		78
6		B	5	2		9	63
7		C or B	5	2		10	10[e]
8		C	1	2		11	84
9		A	3	1.5		12	93

[a] All the reactions were performed at room temperature: method A, oxone in water added to alkene in methanol, uncontrolled pH; method B, same as A, but pH 6; method C, oxone and alkene in water, pH 6. [b] An excess of potassium hydrogen persulfate is necessary, due to competitive peroxide decomposition.[7] [c] Yields are given for isolated epoxides unless noted otherwise. [d] The ratio 7/8 were evaluated by ^1H NMR and GLC coupled with a mass spectrometer; when 1 equiv of $KHSO_5$ was used, 4-vinylcyclohexene was also present in the reaction mixture. [e] Yields evaluated by ^1H NMR.

AG CH-9100 Herisau combi titrator. Oxone is a stable powder containing 2 mol of $KHSO_5$, 1 mol of K_2SO_4, and 1 mol of $KHSO_4$ and is sold in Europe by Aldrich. Cyclohexene, cycloheptene, cyclooctene, cyclododecene, 4-vinylcyclohexene, *trans*-cinnamic acid, and sorbic acid were commercial products. 2-Cyanobicyclo[2.2.1]hept-5-ene and 4-thiatricyclo[5.2.1.$0^{2,6}$]dec-8-ene were prepared following reported procedures.[6,8]

All the epoxides, but the sulfone **3**, were known compounds and had spectral data that where identical with those given in the literature[2,9–11] or with those of commercial samples.

Epoxy sulfone 3 obtained in 86% yield (method A) after column chromatography; recrystallized (CH_3CO_2Et/*n*-hexane, 4/1): mp 241–242 °C; ^1H NMR ($CDCl_3$) δ 3.27 (br s, 2 H), 2.65–3.65 (m, 8 H), 1.5–1.8 (m, 1 H), 0.8–1.1 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 48.4, 48.2, 38.2, 37.7, 26.8; IR ($CHCl_3$) 2960, 1315, 1215, 1140, 850 cm^{-1}.

Anal. Calcd for $C_9H_{12}O_3S$: C, 53.98; H, 6.04; S, 16.01. Found: C, 53.73; H, 5.99; S, 16.02.

Typical Procedures. Method A. A solution of oxone (4.62 g, 15 mmol of $KHSO_5$) in water (20 mL) was added in one portion to a solution of cyclooctene (1.1 g, 10 mmol) in methanol (20 mL). The reaction mixture was then magnetically stirred during 4 h at room temperature. After addition of water (50 mL), the solution was extracted with methylene chloride (2 × 20 mL). The extracts were dried ($MgSO_4$) and the solvent removed in vacuo, affording 1.19 g (94%) of 9-oxabicyclo[6.1.0]nonane (**6**) having spectra identical with those of a commercial sample (mp after sublimation 56 °C, lit.[12] mp 56–57 °C).

Method B. A solution of cycloheptene (960 mg, 10 mmol) in methanol (20 mL) was added in 5 min to a solution of oxone (6.15 g, 20 mmol of $KHSO_5$) in water (50 mL). Before the addition was started the pH was adjusted to 6 and it was monitored with a pH electrode and kept at this value during the entire reaction by dropwise addition of KOH (1 M in water). The reaction mixture was stirred for an additional 4 h and extracted with methylene chloride (2 × 20 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed on a rotatory evaporator. The residue was bulb-to-bulb distilled at 85 °C (50 mm) to give 1.02 g (91%) of 8-oxabicyclo[5.1.0]octane (**5**), giving spectra identical with those of a sample prepared by a reported procedure.[13]

Method C. A solution of oxone (6.15 g, 20 mmol of $KHSO_5$) in water (20 mL) was added in one portion to a solution of sorbic acid (1.12 g, 10 mmol) in water (20 mL) while the pH was kept at 6 by addition of aqueous 1 M KOH. After 1 h of stirring, the pH remained constant without KOH addition. The solution was acidified to pH 1 (12 N HCl) and continuously extracted with ether during one night. The ether extract was dried ($MgSO_4$) and the solvent was removed, affording 1.10 g (84%) of 4,5–epoxy-2-hexenoic acid (**11**) pure by ^1H NMR. A sample purified by crystallization (CCl_4/*n*-hexane) had mp 82 °C (lit.[2] mp 81–83 °C).

Registry No. **1**, 2434-67-5; **2**, 83947-07-3; **3**, 95722-43-3; **4**, 286-20-4; **5**, 286-45-3; **6**, 286-62-4; **7**, 106-86-5; **8**, 106-87-6; **9**, 53897-32-8; **10**, 1566-68-3; **11**, 74923-21-0; **12**, 18776-20-0; $KHSO_5$, 10058-23-8; (*Z*)-cyclododecene, 1129-89-1; 4-vinylcyclohexene, 100-40-3; sorbic acid, 110-44-1; cyclohexene, 110-83-8; cycloheptene, 628-92-2; cyclooctene, 931-88-4; (*E*)-cyclododecene, 1486-75-5; 3-heptene, 592-78-9; *trans*-cinnamic acid, 140-10-3; bicyclo[2.2.1]hept-5-ene-2-carbonitrile, 95-11-4.

(7) Edwards, J. O.; Pater, R. H.; Curci, R.; Difuria, F. *Photochem. Photobiol.* **1979**, *30*, 63.
(8) Stetter, M.; Landscheit, A. *Chem. Ber.* **1979**, *112*, 1410.
(9) Brown, P.; Kossanyi, J.; Djerassi, C. *Tetrahedron, Suppl.* **1966**, *8*, 241.
(10) Shaskov, A. S.; Cherepanova, E. G.; Kas'yan L. I.; Gnedenkok, L. Y.; Bombushkan, M. F. *Bull. Acad. Sci. U.S.S.R., Div. Chem. Sci.* **1980**, *29*, 382.
(11) Carlson, R. G.; Behn, N. S.; Cowles, C. *J. Org. Chem.* **1971**, *36*, 3832.
(12) Cope, A. C.; Fenton, S. W.; Spencer, C. F. *J. Am. Chem. Soc.* **1952**, *74*, 5884.
(13) Gerkin, R. M.; Rickborn, B. *J. Am. Chem. Soc.* **1967**, *89*, 5850.

Diels–Alder and Retro-Diels–Alder Reactions: From *N'*-(Thioacyl)formamidines to Thio Amide Vinylogues

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As part of our continuing study of the chemistry of sulfur-containing heterocycles, we have developed and generalized the cyclocondensation reactions of *N'*-(thio-

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